

POST-GENOMICS, EVO-DEVO AND THE RECURRENCE OF TELEOLOGIC THOUGHT[†]

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Abstract

The post-genomic era raises questions about neo-Darwinian genetic determinism. Instead, open aspects of macroevolution become intelligible by Evo-Devo research. At all developmental levels, self-organization acts robustly towards “wholeness”, as exemplified by organoid technologies. In retinal reaggregates histotypical features are reached along different formative routes. Thus, tissue formation is not merely gene-directed, but channeled by unpredictable external conditions. These insights restrict conceptions of onto- and phylogenesis. Neither is characterized by unlimited randomness nor by finite genocentrism. A re-examination of Driesch’s drive to wholeness, i.e., robustness and intentionality, appears timely, while his teleologic postulates remain undecidable by reductionist reasoning.

Keywords

retinal organoids • robustness • self-organization • standard evolutionary theory (SET) • teleonomy

Introduction: Neo-Darwinism unsettled

The last half century has experienced an unmatched triumph of molecular biology, to which - as their mainstays - genomics, molecular cell and developmental biology, epigenetics and stem cell biology have contributed. Together, these disciplines have led biosciences into the so-called “postgenomic era”. Instead of a narrowed view into the cell nucleus and its DNA, the biologists’ visor has opened onto a dynamically changing cellular environment. Mutual actions between the molecular, cellular, organismic, and up to ecological hierarchical levels - ever up- and downwards interacting - brought into the scene postgenomic concepts of nature. Concomitantly, skepticism about the so-called *standard evolutionary theory* (SET), also known as *population genetics* or *Neo-Darwinism*, became audible (2–4). Indeed, gaps within the standard teaching of evolution had been outlined much earlier (5–7). For instance, proponents of SET had ridiculed ideas of the inheritance of acquired traits, e.g., *Lamarckism*. But notably, exposing flies to heat stress demonstrated that a stress-induced novel morphologic trait could eventually occur in the progeny without applying stress (after about twenty generations), i.e., an individual alteration was now *genetically assimilated* (8). The

field of molecular *epigenetics* reveals that parental acquired attributes can indeed be transferred to their progeny (9,10). For instance, methylation and acetylation of DNA or of histones are effective mechanisms to functionally switch genes on or off (see Fig. 1b: molecular switch). Epigenetic processes depend substantially on the individual’s experiences (e.g., stress, food, climate, etc.), which during a lifetime will imprint a specific epigenetic landscape onto its genome (11,12). Furthermore, epigenetic effects can become fixed in germ cells (13,14), and thus – contrary to *Weismann’s barrier* (10), and occasionally denoted as *Neolamarckism* (see glossary) – be transmitted into the next generation. Thus, epigenetics provides strong evidence against unlimited validity of SET.¹

Nonetheless, how could Neo-Darwinism be established so successfully as a standard theory (SET) during the first half of the 20th century (details in (15–17)? SET is based on Darwin’s two grounding assumptions of random individual change of organisms (mutations), and their subsequent competitive

¹ See for *terms in italic* in glossary.

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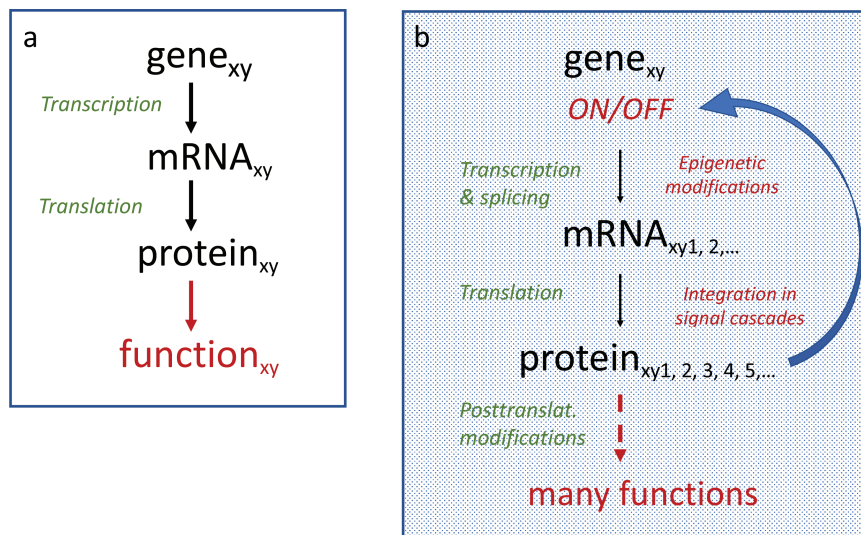


Figure 1. Two concepts of gene action in comparison. – a. The classic concept of *one gene-one protein* was strictly deterministic. The environment (including the inner milieu of the developing embryo) remains irrelevant (white background). A particular gene, and its coded protein were assigned only one function. – b. According to a postgenomic conception, one gene can code for more than one protein, and be involved in many functions. Note feedback effects on gene switches (ON/OFF; blue arrow), which are derived from many environmental sources (dotted blue background; misses in a.).

selection (fitness differences leading to cumulative differential reproduction; (18,19). First, it was an advancing knowledge of chromosome structure as well as of the chemical nature of genes, and the comprehension that selection takes place predominantly at the level of populations (16). Accordingly, new species arise through changes in the gene pool of populations. Following the model of allopatric speciation (holding for the bulk of animal species (10)), this occurs in a way that a population is split, for instance by expanding ice shields. Further on, both subpopulations will develop divergently, and – at a later contact of their individuals – will not mix again. As Ernst Mayr expressed the point “*the individual mutates, and the population evolves*” (16). Notably, Darwin’s two basic assumptions were not touched substantially. Neo-Darwinism traced phenotypic changes back to the level of genes, thus to spontaneous changes of DNA sequences. From bacteria it was well known that mutations occur randomly. Accordingly, it stood to reason to propose random genetic changes for all organisms; moreover, the genetic transmission of alleles in sexually reproducing organisms is distributed stochastically within their progeny (*recombination*). This in turn led to the far-reaching postulate that evolutionary change occurs purely at random, and over long evolutionary periods should occur evenly and slowly (*gradualism*, see glossary), much as Darwin had imagined. In particular, the postulated randomness of the individual genomic sources of variation led to the assumption that evolutionary change would proceed entirely without direction (20). Only later would this concept

lead to interpretative difficulties since it adhered to a narrowed understanding of gene functioning (see below; Fig. 1).

1. The dead end of genetic determinism (geno-centrism)

Eventually, Neo-Darwinism was drawn into a momentous dead end through the “*one gene-one protein dogma*” (Fig. 1a; 16). As a standard point of view until into the 1970s, this conception, while comprehensible in its original Beadle-Tatum formulation (21) led to a fallacy within Neo-Darwinism, namely, that there existed a fixed relationship between the genetic makeup (genotype, or genome) and the phenotype of an individual. While this dogma may (partly) apply for simple organisms, it rarely reflects the functionalities of genes of eukaryotic organisms, e.g., developmental genes of plants or animals (cf., Fig. 1b). This is because genes often code for several different proteins, where each could subserve several different functions, and which in turn can interact via complex reaction networks in diverse manners (22). Thus commonly, genes are involved in the shaping of several features (*pleiotropy*). Findings of epigenetics render the spectrum of regulated gene actions and their effects at the phenotypic level even more complex (briefly mentioned above). On top, we may ask whether there is a fixed phenotype at all, when all organisms keep changing at every instant (physiology, growth, degeneration, behaviour, etc.)? In fact, the theory of

process ontology perceives living organisms (in fact the entire universe) not as three-dimensional objects or things, but rather as ever interacting processes, asking for a complete rethinking of evolution (23). Clearly, the realization of genetic activities depends therefore predominantly on specific spatio-temporal environments (24). Hence, gene expression turns out to be a highly non-linear process (see below), exhibiting not one-to-one, but many-to-one and one-to-many causal dependencies and relationships.²

Indeed, in retrospect it is astounding how from the beginning of the 20th century onwards Neo-Darwinism could turn aside valid objections by established biologists from various fields (3,6,7,17,25,26); see glossary, *epistemic closure* (27)). As only one example, briefly consider the concept of gradualistic evolution. Based upon the fossil record, the course of evolution presents itself as everything but slow and continuous. Long periods of stability persisted, which were followed by short periods during which individual features changed drastically. In particular, the so-called *Cambrian Revolution* about 540 mya ago was a period of “productive instability”, during which practically all presently existing major animal groups (approx. 35; (10,28,29) appeared within a short period of time. Later, similar phenomena of rapid diversification re-occurred several times. After massive waves of extinction (in particular, *the big five*), each time the animal kingdom has regenerated swiftly, whereby the major *bauplans* existing since Cambrian times emanated into ever new forms which then could exist unchanged over long periods. Gould and Eldredge have explained the phenomenon of long periods of stasis interrupted by relatively short periods of extinction and regeneration by their concept of punctuated equilibrium (*punctualism*; theory of disrupted equilibrium; (29). During periods of stasis representing the default state of nature, species would remain mostly unchanged. Notably, the ornithologist Otto Kleinschmidt discovered that it was not continuous change and drifts of avian populations, but rather their persistence (stability, constancy, stasis and coherence) characterizing their essence (30).

For instance, the white wagtail (*Motacilla alba*) has presumably existed without any change for at least 60 million years. Moreover, Kleinschmidt realized that certain features of a bird’s population (e.g., beak shape, patterns, colors of plumage) varied within a given local area, but - notably - without presenting a distinct maximum within that sample (Fig. 2; called *Formenkreise*, what Ernst Mayr later denoted as *superspecies*). As soon as birds were dwelling in urban areas, or even more so, when bred as domestic animals (e.g., urban, homing pigeons), the band widths became wider,

while their distinct features became blurred, thus questioning Darwin’s postulate that evolution could be compared to animal breeding (see for details, (31). Only when populations come under pressure by extreme conditions (e.g., stress, environmental catastrophes, etc.) the equilibrium becomes distorted, followed by rapid variability and emergence of new species.

This pattern, which occurs repeatedly over Earth history, suggests a non-random sequence of events. The conquest of land by flora and fauna exemplifies a directed evolutionary step (1, 32). It can be shown that for a successful transition, the land not only first needed to be settled by plants to exploit minerals from the soil, but in addition, plants had to develop elongated, vertically high rising forms to prepare the atmosphere for animals living on land. With this, plants abandoned their spherical shape, which had been well established in the aquatic milieu (e.g., Volvocales), and transformed for a predominantly elongated growth on land. Animals, on the other side, could further differentiate their round shape, which originates from the egg, to further develop it into diverse adult forms. If we consider how life on land became evolutionarily possible for animals, this temporal sequence accompanied by morphologic adaptations on the plant’s side were mandatory. Thus, it is the given physical earthly structure, not the genes alone that decided whether and when animals could move on to the land. Fields and Levin propose that the entire course of evolution could be conceived as a planetary developmental event, whereby at all organismic levels strong attractors direct the non-random emergence of - what they call - *target morphologies* (33). Accordingly, Conway-Morris presumes that, if biologic evolution on this planet would be repeated, the same organismic groups including humans would reoccur in a similar sequence (*convergence*, (34)).

2. Evo-Devo renders macroevolution intelligible

The appearance of new morphologic constructions raises the question, how can fundamental novelties develop during evolution, such as a placenta or mammary glands with mammals. Could it suffice to accumulate minor changes from generation to generation (*microevolution*) to achieve eventually a major transformation (*macroevolution*)? Hitherto, Neo-Darwinism could not provide a satisfying answer. Instead, isn’t it more likely (even necessary) that some complex novelty appears abruptly on the scene, like a phoenix from the ashes, which immediately presents new functional possibilities and target points for a transforming selection (see also threshold model, (35)? In this respect, discoveries of molecular developmental biology provide remarkable progress with a research program, which has become known

² Evo-Devo is acronym of *evolutionary developmental biology*.

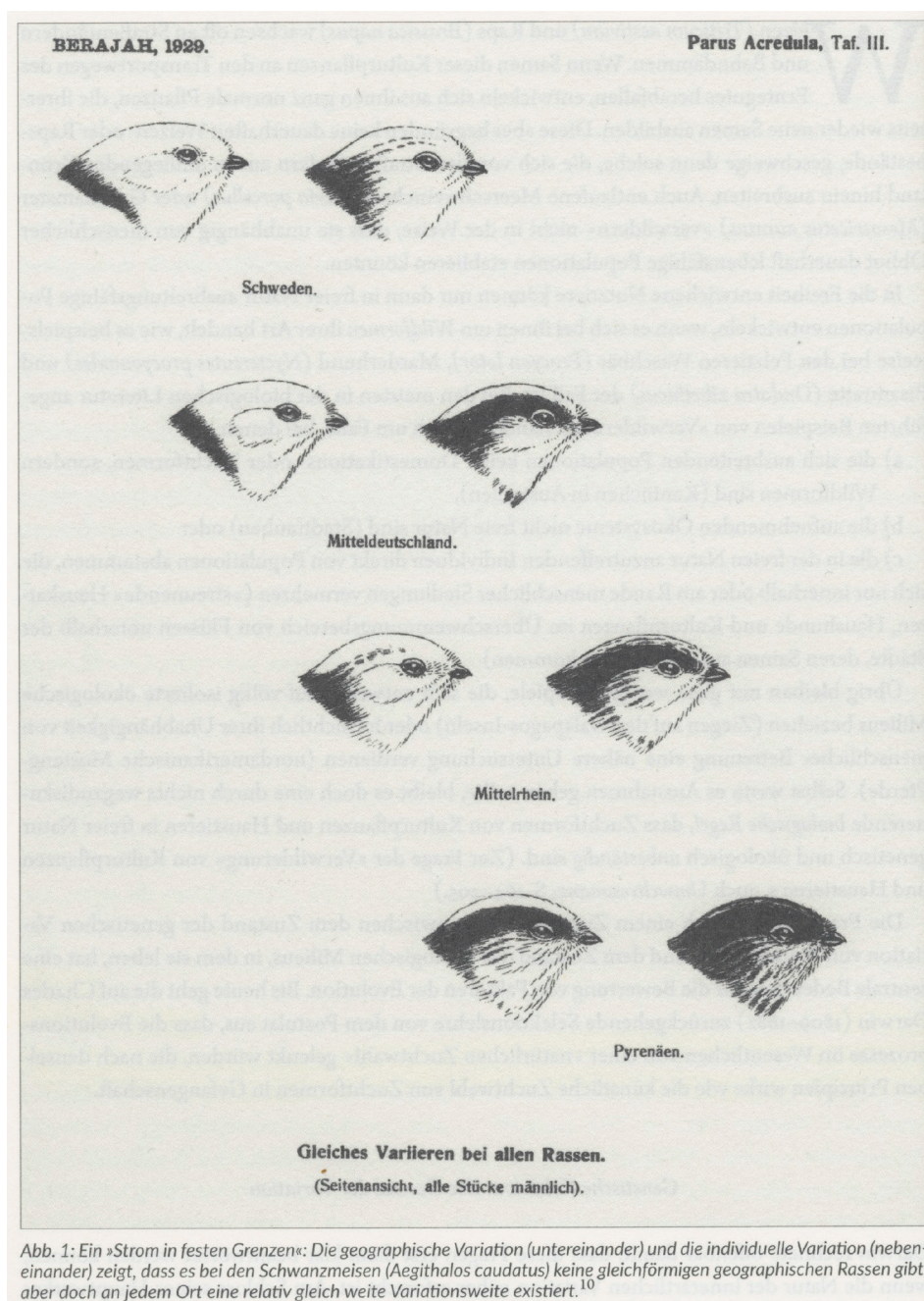


Figure 2. Avian *Formenkreise* as analyzed by Otto Kleinschmidt (denoted as “super-species” by E. Mayr), exemplified here with the long-tailed tit (*Aegithalos caudatus*): regional variations are arranged vertically from Sweden (on top) to the Pyrenees (bottom), while variations within local populations are presented side by side (30,31).

as *Evo-Devo* (17,28,36–38). Here, this exciting field can be highlighted only with a few sentences.

The development of most eukaryotic organisms depends on a manageable number of important developmental genes

and molecular signal cascades (10). This molecular basic set-up, also known as a molecular toolbox (*tinkering*), existed already before the Precambrian period and has been highly preserved until the present. These molecular tools regulate ontogenesis of plants and animals in a combinatorial manner,

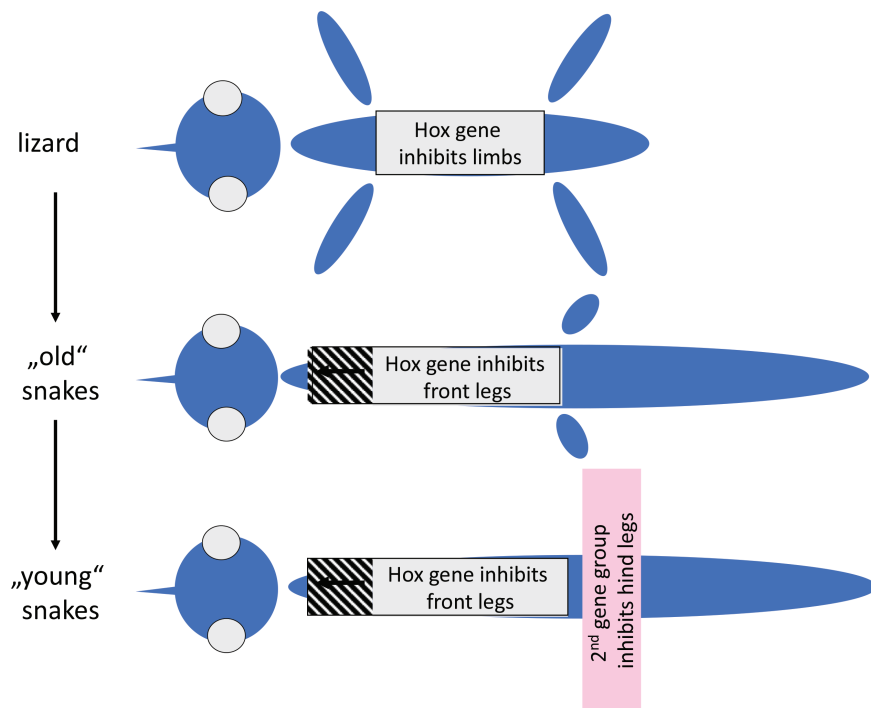


Figure 3. Evo-Devo can (in theory) explain a macroevolutionary transition from a saurian to a serpent's *bauplan* by only two mutational steps of master genes (scheme, simplified): in step 1 expression of a Hox-gene is extended toward the front (anteriorly, left), suppressing formation of front legs, thereby achieving an evolutionary status of limb reduction as revealed in ancient snakes (e.g., pythons, boas; their skeleton still presents remnants of pelvis girdle and hind limbs). In step 2, a 2nd master gene inhibits formation of hind limbs, a status found in young snakes (e.g., vipers).

where a particular molecular module can exert different functions in different organisms; this applies even for different places or times of action within the same organism (Fig. 1b). If mutations of single components of such molecular networks occur, then this can entail - at best - meaningful or functional transformations of the phenotype (Fig. 3, possible transformation from a saurian to a serpent habitus; cf. below, polydactyly). Thus, an abrupt branching of the phenotype can become intelligible based on only minor changes of the genotype (see more examples in (24,39–41). Hence, preconditions for the origin of new forms are fulfilled, i.e., for macroevolution. In this respect it is of utmost importance that the respective environment (molecular, cellular, up to ecological) can canalize ("bias") such processes, and - as constraints - can even initiate them by feedback actions on the genetic material (cf. Fig. 1b, blue arrow; see Fig. 4, four-legged bird).

Given this restricted molecular toolbox, then formation of bodily patterns should become easily predictable. Indeed, computer simulations based on molecular reaction-diffusion mechanisms can model natural patterns at high fidelity and

impressive esthetic beauty (42–44). The interplay between longranged inhibitors and local autocatalytic activators can reproduce – besides others – repetitive threshold values, leading from gradually changing patterns to bifurcations, producing borders, dots, stripes, or duplicate them, whereby the particular outcome depends on minor changes of parameters.

However, simulations and real life are different topics, since only rarely in development situations might exist, where the interplay of two molecular factors alone will cause a certain phenotypic feature. Rather, seemingly simple phenotypic characters often depend on complex environmental networks (from molecular up to organismic levels). For instance, formation of digits on hands and feet, and their quite frequent malformations, known as polydactyly, depend on a rather large number of molecular factors (e.g., Shh, Wnt, Fgf8, retinoic acid). But notably, fields of digit cartilage formation are not defined by diffusion of morphogens. Rather, bistable states of neighboring cells determine their numbers, as revealed by a threshold model for polydactyly (9,35). The respective ON or OFF states can depend on only a few factors, with

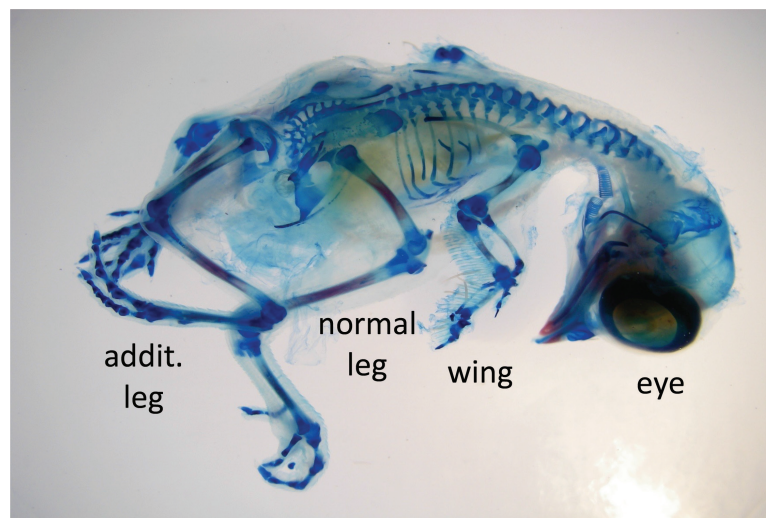


Figure 4. Modular phenotypic change in a bird with additional pair of legs at its hind end documents “Evo-Devo in action”. Supposedly, only minor genetic changes have caused these drastic malformations, e.g., induced by hormonal stress (c.f. also Fig. 3). Note normal morphology of additional legs (see text: *drive to wholeness – holism, teleonomy*). Evidently, such a malformation will not provide any survival advantage, and thus will not evolutionarily persist. Yet this specimen exemplifies the occurrence of abrupt and far-reaching alterations (specimen and photo: laboratory of author).

minor genetic alterations causing additional threshold peaks, which will cause supernumerary digits. Certain numbers of discrete characters occur preferentially, i.e., their distributions are biased (cf., the “missing variant” of centipedes; (28). Evolutionarily, polydactyly shows that novel morphological entities can occur abruptly in a one-step manner. Phenotypic variations i) are driven towards modular wholeness (see also Fig. 4, supernumerary chicken leg pair), and ii) can occur discontinuously, supporting *punctual* macroevolution (45).

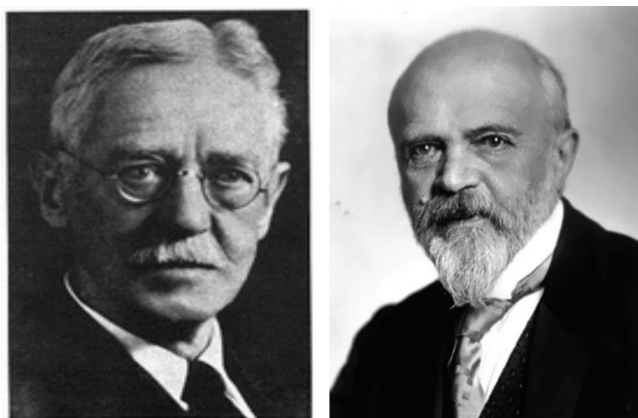
3. Biased emergence: The vertebrate retina as a self-organizing *in vitro* model

In fact, multiple examples from the field of regeneration biology present aspects of target-directed self-organization, which could be conceived as *bias of development*, as *directionality*, or, as a *drive to wholeness* (see glossary; (10). Historically, the famous *Schüttelversuche* by Hans Driesch at the end of the 19th century set a cornerstone to embryology known as *embryonic regulation*, by analyzing the behavior of dispersed cells from the 4- to 8-cell stages of sea urchin embryos. As a former student of August Weismann (see *Weismann’s barrier*; (10,27), Driesch expected that from each individual cell – if anything – only parts of an embryo should develop, e.g., only muscle, or nerve tissue, etc. To his perplexity, however, he found that *whole embryos*, including all cell types, could develop from an individual cleavage cell. Today, this phenomenon is conceived as a genetic de-differentiation

of individual cells into the state of a fertilized egg, a return to (nearly) the zygote, which as an early embryonic stem cell then can generate a whole larva under the given *in vitro* culture conditions. With his discovery, Driesch laid the grounds for regeneration biology and eventually to stem cell biology.

Another striking demonstration of an inherent systems property to maintain wholeness was provided by Fankhauser’s famous study on the regulation of cell size (46). Some variants of newts are found with more than a double set of chromosomes (*polyploidy*). Fankhauser found that as polyploidy increases, the cell size increases in all tissues, while the total size of the animals remains unchanged. This effect was particularly obvious in the larvae’s pronephric canal (precursor of kidneys). Even Albert Einstein was puzzled by this finding and drove him into puzzlement; he noted „...*The importance of the cell as ruling element of the whole had been overestimated previously. What the real determinant of form and organization is, seems quite obscure*” (cited from (47). Clearly, in this instance a drive to achieve a certain body size, i.e., a certain wholeness, cannot be neglected.

Whether considering normal development or regulation, it is difficult to distinguish experimentally *nature* from *nurture* effects in forming a complex tissue. Let us consider, for instance, the making of a vertebrate retina. In all vertebrates, eye cup formation and the ensuing differentiation of retina and pigmented epithelium (RPE) follow molecularly and histologically similar, seemingly determinative paths. But



Henry Van Peters Wilson
Marine Lab John Hopkins U.
Bild: <http://beaufortartist.blogspot.de/2008/03/origins-of-marine-lab.html>

Hans Driesch
www.liberliber.it

Figure 5. H. P. Wilson and H. Driesch – two widely forgotten fathers of regeneration and stem cell biology. Driesch was the eminent proponent of *Neovitalism*.

are these processes indeed purely autonomous and target-directed (biased)? If one attempts to analyze them in absence of external factors as acting *in vivo*, *in vitro* experiments using dispersed cells from a certain tissue are instrumental, to then follow their behavior in a rotating *in vitro* culture set-up (Schüttelversuche). Studies on histotypic reaggregation of embryonic stem cells from the avian and mouse retina were telling, which historically can be traced back to researchers like Wilson and/or Driesch (Fig. 5), and eventually contributed to the breakthrough of current stem cell biomedicine (reviewed in (48–50).

Since the early 1950s, Malcolm Steinberg and Aaron Moscona had – independently from each other – discovered histotypical structures in reaggregated cell spheres from the chick embryonic retina (reviewed in (51). The vertebrate retina is particularly suited as a model tissue for such studies, due to its simple cell type composition, its threefold laminar structure, and its easy access (Fig. 6d, right; 7e). Briefly, all cell bodies are arranged in three layers: an outer (ONL), an inner nuclear layer, and a ganglion cell layer (GCL). The ONL holds photoreceptors consisting of rods and cones (note: ratios of rods, and types and ratios of color-sensitive cones, vary in different species), horizontal (HCs) and bipolar cells (BCs) constitute the INL, and ganglion (GCs) and displaced amacrine (dACs) cells compose the GCL. Within two synaptic layers, called outer plexiform (OPL), and inner plexiform layer (IPL), PRs connect with BCs and HCs in the OPL, and BCs with ACs and GCs in a multilaminar IPL (further see below). Radial Müller glial cells (MC), that span through the entire

width of the retina, have tremendous developmental and physiological impacts.

Depending on the species (avian, Fig. 6; mammalian, Fig. 7), the chosen culture conditions, in particular the composition of the culture media (salts, growth factors, sera, etc.) and the type of rotation, the emerging histologic structure within forming *retinospheroids* can be altered (Figs. 6, 7). With chicken embryonic retina (Fig. 6), dispersed cells quickly reaggregate and begin to sort out. As a first sign of self-organization, internal rosettes will form holding mitotic cells and (later) future PRs (Fig. 6b, c). In between rosettes, INL cells become neatly arranged, which surround a cell-free space (Fig. 6c, e), resembling an IPL (here called *ipl*). As *in vivo*, so-called starburst amacrine cells (SACs) are the first to differentiate, which send their neurites into the *ipl*. Amazingly, they form two synaptic subbands, which lay the grounds for further complex *in vitro* IPL network formation (Fig. 6e).

Notably, dispersed cells from the neonatal gerbil retina (Mongolian desert rat) behave differently. Rosettes are not found; instead, already in minute spheroids SACs begin to sort out, arrange pairwise and send out processes to organize an IPL network (Fig. 7a-c). As another leading process in both species, the inside-out polarity of reconstituted segments of layers could be reverted, depending on media supplements (e.g., RPE, or MCs, cf. Fig. 6b, d), eventually leading to nearly fully laminated spheroids. With chick retina, RPE induced a reversion from rosetted to fully stratified spheroids (Fig. 6b, d), leading to a normal laminar spherical composite *in vitro* (*retinospheroid*; now generally called *retinal organoid*, (50). With gerbil retina (Fig. 7), addition of RPE induces a laminar spheroid with the GCL, IPL and INL oriented outside (Fig. 7d, cf. 7a). A combination of RPE and Wnt-3b again reverts the layering to produce a fully laminated spheroid, achieving an advanced IPL towards its inner core (Fig. 7f).

These findings documented for the first time (52), that originating from dispersed stem cells a) it is possible to reach a nearly complete retinal tissue formation *in vitro*, and that b) this phenomenon not only depends on retinal genes alone, but as well on the prevailing culture conditions (e.g., neighboring cells, growth factors, etc.). In both species, a complex *ipl* network formation revealed that – dependent on the chosen *in vitro* culture conditions – different developmental paths can lead to a similar target (e.g., *many roads to Rome*; (53), namely a wired IPL-like network. Even if a complete laminar structure was not achieved in each experimental set-up, cells within their artificial surrounding were always biased towards retinal wholeness. The cells were “attempting to build” a structured retina. This is what Fields and Levin mean with “target morphology” – an attractor

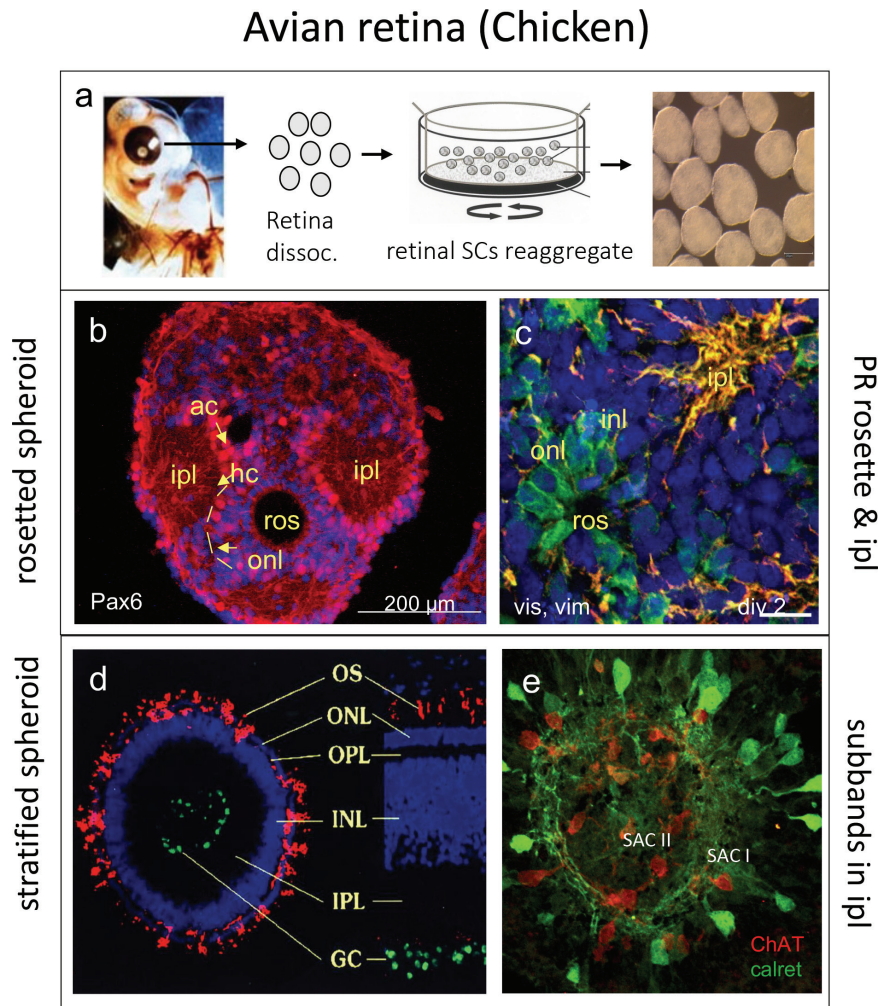


Figure 6. Target-directed self-organization in reagggregated spheroids from chick embryonic retina, initiated by cells of outer retina. A. experimental set-up (left, 6 days-old embryo; right, reagggregated spheroid); b. section of “rosetted spheroid” (cf., right in a), presenting PR rosettes (*ros*), and IPL-like synaptic areas (*ipl*); c. higher magnification of a rosette (*ros*) and a close-by *ipl*; d. so-called *stratospheroid* with correct and complete laminar organization, *onl* is outside and *gcl* is inside (d. on right, chicken retina for comparison); e. enlarged *ipl* presenting formation of synaptic subbands. Stainings: DAPI (blue) for cell nuclei; b. Pax6 (red) for Acs; c. visinin (green) for PRs; vimentin (yellow) for MCs; d. CERN901 (red) for PRs, dACs (green); e. calretinin (green) for Acs; ChAT (red) for SACs. Note different magnifications in a-e. **Abbreviations:** INL, ONL, inner and outer nuclear layer; GCL, ganglion cell layer; IPL, OPL, inner and outer plexiform layer; PR, photoreceptor; HC, horizontal cell; BP, bipolar cell; AC, amacrine cell; dAC, displaced amacrine cell; SAC, starburst amacrine cell; GC, ganglion cell; ChAT, choline acetyltransferase; *ros*, cell rosette holding mitotic cells and/or photoreceptors. Figs. 6a, b, d from (1); Figs. 6 c, e from (64).

that directs the organization of tissue formation non-randomly at various levels (33).

4. Genomic potential, indeterminable environments and teleonomy

Such a target directionality could not be denied. In all instances it became evident (Figs. 6, 7) that not only genes

direct developmental processes, but the given cellular environments set multiple switch points to reach a final tissue structure. Thus, development is a product of gene actions interacting with cells, tissues and with the environment to result in emergent features. Accordingly with such *in vitro* retinal approaches, self-organizing emergent processes presumably direct the outcome of each experiment (53). The number of possible environmental parameters and each of their prevailing impacts are immense, and therefore *de facto*

Mammalian retina (Gerbil)

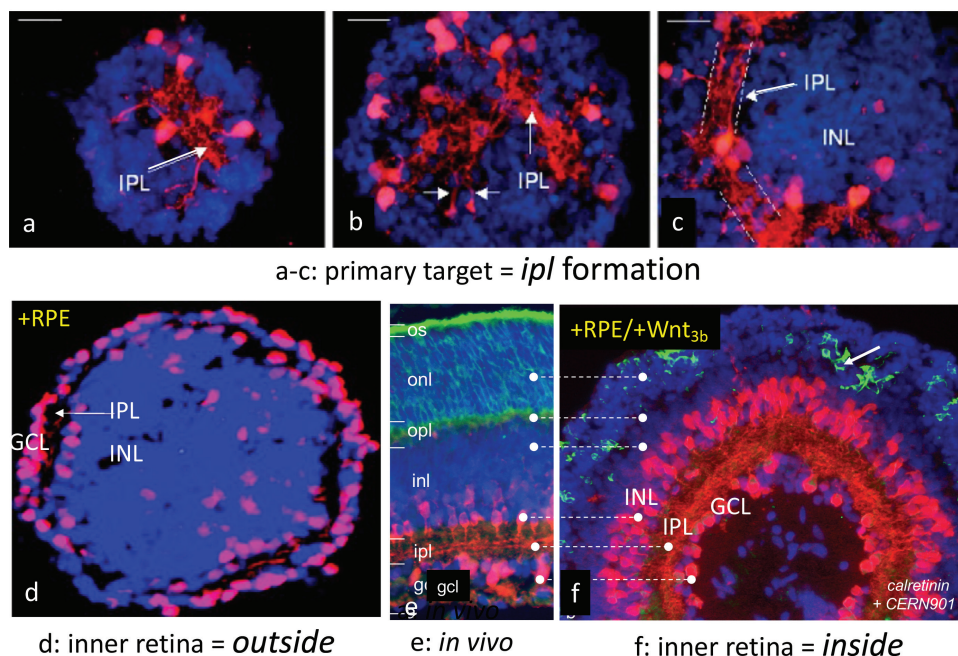


Figure 7. Alternate routes of target-directed self-organization in reaggregated spheroids from a mammalian neonatal retina (Gerbil, Mongolian desert rat), initiated by cells of inner retina. A-c) *ipl* formation is leading target (not PR rosettes, as in Fig. 1): in control reagggregates, calretinin+ ACs (red) sort out and begin to organize an *ipl*, including synaptic subbands (at 7, 9, 12 dic., resp.); d) inside- out laminar retina: in presence of RPE, all ACs and dACs plus their *ipl* become arranged under surface (outside) of spheroid; HCs and few PRs are found inside); e) shows *in vivo* gerbil retina at P9 for comparison; f) correct laminar structure and advanced *ipl* differentiation: addition of Wnt-3b and RPE counteracts laminar inversion (as seen in d), and promotes *ipl* differentiation. Stainings: calretinin+ (red) for ACs and dACs; CERN901 (green) for PRs. For abbreviations., see legend to Fig. 6. Figs. 7a-d from (65); Fig. 7e, f from (66).

are not controllable. Notwithstanding, the often-observed target orientation and accuracy with many developmental processes are perplexing. To avoid the term *directionality*, generally the term *robustness* of biologic processes is preferred (27,54). For warranting a normal course of development *in vivo*, it is robustness which acts as its foremost directive. Irrespective of countless developmental possibilities, which were – in principle – realizable on basis of the given genome and its associated molecular modular networks (which could be called the individual “genomic potential”), the realized developmental path will be channeled and restricted (i.e., biased) by the actual spatiotemporal environment. Not genes alone, but the environment channels and secures robustness (55).

This characterizes what in the present context is meant by self-organization and emergence (56–58), and what Kirschner *et al.* describe when they speak of a universe of possible phenotypes: “The genotype, however deeply we analyze it, cannot be predictive of the actual phenotype, but can only

provide knowledge of the universe of possible phenotypes. Biological systems have evolved to restrict these phenotypes, and in self-organizing systems the phenotype might depend as much on external conditions and random events as the genome-encoded structure of the molecular components” (cited from (59)).

The insight, that genes alone do not determine ontogenesis and phylogenesis, brought Kirschner and colleagues to their provocative title of “molecular vitalism” of their above-mentioned article. They conclude that “At the turn of the twenty-first century, we take one last wistful look at vitalism, only to underscore our need ultimately to move beyond the genomic analysis of protein and RNA components of the cell (which will soon become a thing of the past) and to turn to an investigation of the “vitalistic” properties of molecular, cellular, and organismal function.” How can modern cell biologists speak of *vitalism*, a concept holding that living organisms would be driven by vital forces, and which had completely vanished after the advent of Darwinism?

In fact, it was Driesch who had revitalized these ideas to become founder of *Neovitalism*. When he had summed up his findings by the telling sentence that “*the prospective potency of a blastomere is higher than its prospective fate*”, then it was not defined cell fates which determined the future of his cells in a glass dish, but – as Driesch postulated – somehow rather a certain *knowledge*, an *image of wholeness*, resident in each blastomere, which directed the generation of a complete organism. For Driesch himself his observations were most bewildering, entirely overturning his worldview. He could not manage to explain them on a purely reductionist basis, but he postulated a non-material, transcendental *Lebenskraft* (vital force, gk. *Entelechy*, according to Aristotle), supposedly residing in each cell and entailing a “drive to wholeness” (*holism*; (27)). His neovitalistic holism was also denoted as *teleology*. Based on modern conceptions of self-regulating complex systems, probably most (if not all) of these phenomena can be perceived as *robustness*, and would figure under *teleonomy*, which denies – in contrast to *teleology* – any metaphysical influence on target-directed, purposeful processes.

What precisely do Kirschner *et al.* mean with their vitalism? Do they make another turn to transcendence, as Driesch did? No, certainly not. Yet, like Driesch, they insist that living organisms cannot be fully explained on a purely mechanistic or “bottom-up” physicalist basis, and that the often-applied machine comparison fails (see also Discussion in (58)). They wonder how in a potentially non-deterministic world the development of organisms and their physiology can reach their admirable robustness, which appears to suggest vitalist forces. Since they repudiate an *Entelechy*, that is, a transcendental vital force, they rely on explaining the chemical basis of robustness by applying methods of artificial intelligence (AI). They hope that interactions between countless molecular-genetic networks with indeterminable environmental influences may become decodable, to then discover the causes of biologic robustness, eventually even decoding the phenomenon of life (s. also (22,23,57,60)). Accordingly, these authors do not advocate for a transcendent vitalism, but take a *teleonomic* view of complex emergent processes in nature.

5. Biology in an open universe

The post-genomic era has realized that expression of many genes is environmentally directed (see glossary: *Nature-vs.-Nurture-discussion*, *phenotypic plasticity*; Fig. 1), to which research on Evo-Devo and epigenetics have substantially contributed. Their discoveries finally revealed that the standard teaching of Neo-Darwinism (SET, modern synthesis, population genetics) requires supplementation by

an *extended evolution theory* (EET; (3)). Some authors were even speaking out for a complete restart of evolutionary theory (3,4,17,37,55). For instance, Ron Amundson stated (17) “*Developmental types and exclusive population thinking are incompatible. One or the other (or both) must go before a new synthesis is possible*” (whereby *developmental types* refers to Evo-Devo, and *population thinking* to SET). Even if the genomic potential of each individual organism – under all random influences occurring during its ontogeny – would suggest an infinite number of possible phenotypes (estimates reach numbers more than the number of atoms in the entire universe; see also, (22,60)), then evolution still proceeded anything but purely randomly. Directed during ontogenesis by a restricted number of molecular-genetic networks, the evolutionary events are neither fully determined, nor are they completely random, since evolutionary history ever was and remains environment-dependent. Novel forms act back on and shape their environments. Evolution presents signs of abrupt breaks and biased advances. Its future proceeding as well as its final aim cannot be predicted.

Anyhow it appears – with respect to the complexities of organic structures – that with the appearance of *Homo sapiens* and the outstanding performances of its brain, evolution has reached a unique target state, since the human brain generally is considered the most complex structure in the universe.

Both, during individual development (ontogenesis) as in evolutionary history (phylogenesis), we can observe a *drive to wholeness*. In ontogenesis (as well as during regeneration phenomena) it is a drive to produce a whole organism (or, entire structures, see Fig. 4: the additional pair of legs at the bird’s caudal end as an individual extremity presents wholeness, being formed as threefold structure). Phylogenesis could be conceived as one targeted developmental process, extended over the entire period of life on earth (33). Thus, in both spheres – ontogenesis and phylogenesis – a procedural directionality becomes apparent. What under Driesch was considered as teleology and vitalism, nowadays is debated under the names of teleonomy and robustness. Notably, the term teleonomy is not instrumental to reach a philosophical conception of evolution since it cannot resolve basic questions of causality and finality. The origin of life on earth remains unsolved, whether from a primordial soup, or germs from outer space (61), and whether the final aim of evolution is the emergence of *H. sapiens* – as is often presumed – also remains undecided. Notwithstanding that evolution appears to some scientists and philosophers as clearly biased (62), the concept of *teleology* must be considered as scientifically inappropriate, since it does – as defined above – assume transcendental influences on natural phenomena.

Yet, questions regarding teleology and vitalism are neither absurd nor illegitimate: they do constitute the core of philosophical thought on nature. So, one wonders whether in a causally open world the phenomenon *life* can be scientifically resolved at all. Living creatures do present specific and inextricable features. Do these features represent specific signs of vitalism? In his engaging book *Purpose and Desire*, Scott Turner characterizes life as “*striving for something*”, a postulated feature that all living objects are aiming at something, i.e., are characterized by some *intentionality* (27). He points out that questions of teleology and vitalism are scientifically still timely (see also (23,54)).

Unfortunately, they put the biologist into the dilemma of a destructive dilemma: either a) one performs science legitimately, i.e., strictly by materialistic methods and reasoning, or b) one integrates transcendence into one's thought, therewith avowing oneself as a vitalist, to leave the field of accepted natural science. Science cannot solve this problem. In the post-genomic era, the following conclusions appear to be important: that a) questions of teleology and vitalism are still prevailing, while b) they cannot be answered scientifically; thus, c) biologists should content themselves with these insights. While the popular idiom of *survival of the fittest* aptly reflects and justifies our turbo-capitalist's world, Evo-Devo research has more appropriately converted it into *arrival of the fittest*, adapting to the discovery that the first step to evolutionary change must happen in the embryo (10,17). Post-genomic considerations reveal that onto- and phylogenetic processes are neither purely random nor fully determined, but certainly they represent directed events. The question whether it is more genes that change their environments, or whether possibly it is more so the other way round, is worthwhile contemplating (23,63).

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GLOSSARY

Process & terms	Explanation
Assimilation, genetic	Environment-dependent phenotypic alterations, which are inherited and fixed in progeny.
EcoEvo-Devo	<i>Ecological</i> Evo-Devo processes, directed by environmental conditions.
Environment	as used in here, does not only refer to external surrounds of an organism, but internal environments, from molecular to cellular to organismic, etc.
Epistemic closure of SET	Mindset of SET proponents to neglect opposing arguments (see 20).
Constraints	Development-dependent restrictions on evolution, i.e., physical, or morphogenetic constraints; c.f., <i>tinkering</i> .
Epigenetic patterns	Individually acquired molecular changes on DNA or histone levels; epigenetic patterns can be passed on; contradicts <i>Weismann's barrier</i> .
Gene duplication	Important for evolution: entire families of related genes originated via gene duplication (i.e., Hox genes). One of the two duplicated genes first can be redundant to only later take on a certain new function.
Genocentrism	Gene-centric determinism of NeoD, postulating that the genotype exclusively determines the phenotype.
Gradualism	Concept that evolutionary change occurs at a slow and steady rate; opposite to <i>punctualism</i> .
Holism	Here: tendency to establish whole structures (<i>teleonomy</i> ; cf. Fig. 4).
Hox genes	Important family of developmental genes (master genes). On gene level they present a conserved <i>homeobox</i> (sequence of 180 nucleotides), on protein level a <i>homeodomain</i> of 60 amino acids.
Genotype	Genetic outfit of an individual.
Canalization	Conditional regulation of development; e.g., by environment; c.f., <i>constraints</i> .
Convergence, evolutionary	Independent evolution of similar features in non-related organisms, to adapt to similar environment.
Macroevolution	Large and abrupt morphologic changes of species in evolution.
Microevolution	Minor evolutionary alterations; c.f., <i>Macroevolution</i> .
Modularity	Not only morphology is modular, but also many DNA regions, which can function as <i>enhancers</i> .
Mosaic theory of animal development	August Weismann's postulate, according to which the later cell fate (the cell type) is fixed right after fertilization in so-called cleavage cells. In most cases, this presumption is false.
Nature-vs.-Nurture Discussion	Question of relative influences of the genome versus environment on development and life of organisms.
Neodarwinism	Standard theory of evolution (SET), as developed in the 1st half of 20th century.
Neolamarckism	Epigenetics shows that environmentally-acquired individual traits can - under certain circumstances - be passed on into the next generation.
Organoids	Spherical (3D) cell constructs cultured from stem cells, which resemble histotypic tissue or organ structures; cf., <i>cell spheroids</i> .
Parsimony, molecular	„Molecular toolbox“: Development works with (is achieved by) a restricted set of genetic and molecular networks.
Phenotype	Morphologic appearance of an organism; the organism „as a whole“.
Plasticity, phenotypic	Environment-dependent morphologic adaptation, i.e., jaw size dependent on diet; becomes genetically fixed.
Pleiotropy	Capacity of a gene to code for various functions in different cells.
Ploidy, degree of	Number of sets of chromosomes in a cell, e.g., <i>haploid</i> , <i>diploid</i> , <i>polyploid</i> = single, double and more than double set of chromosomes.
Punctualism	Opposite of <i>gradualism</i> , see above.
Regeneration, biologic	Regeneration of a whole bodily structure from few (stem) cells, i.e., regeneration of lizard tail.
Robustness	Property of developmental processes to reliably (re-)establish a certain target structure; cf. <i>teleonomy</i> .
Teleology	Directionality of biologic processes, incl. metaphysical “vital” forces; distinction to <i>teleonomy</i> ; see next.
Teleonomy	Directionality of biologic processes, driven by natural forces; opposite to <i>teleology</i> .
The Big Five	5 major periods of mass extinctions at approx. 440, 365, 250, 210 and 65 mys ago.
Tinkering, with „toolbox“	Spatio-temporal expression of identical or similar genes (or their resp. proteins) can lead to alternate phenotypes, through mechanism of: • Heterotopy (gene expression at different locations of embryo), • Heterochrony (g.e. at different times), • Heterometry (g.e. defines size or shape of a structure), • Heterotypy (g.e. alters respective protein structure).
Vitalism, biologic	Meaning here: Life conceived as unique unseizable phenomenon, influenced by some transcendental vital force; cf. <i>teleology</i> .
Weismann barrier	Weismann's obsolete postulate of segregation of early germ and somatic cells; e.g., that genetic information is passed on exclusively via the germline, without any influence from environment; c.f., <i>epigenetic patterns</i> , <i>Neolamarckism</i> .